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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,855	11/02/2005	Patrick Van Berkel	089995-000000US	4048

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER

HIRIYANNA, KELAGINAMANE T

ART UNIT	PAPER NUMBER
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1633

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06/01/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/531,855	Applicant(s) BERKEL ET AL.	
	Examiner Kelaginamane T. Hirianna	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 16-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 and 16-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response filed on 07/20/2006 in response to office action mailed on 04/19/2006 has been acknowledged.

Claims 6, 16, and 21 are amended.

Claims 1-13 and 16-22 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6, 11 and 13 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-6, 11 and 13 as written, do not sufficiently distinguish C1 inhibitor as it exists naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated " or "recombinant" before C1 inhibitor. See MPEP 2105.

Claim Rejections - 35 USC § 112

Claims 1-13 and 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a C1 inhibitor that is changed in its circulatory half-life by a O-linked carbohydrate modification in vitro and a method of in vitro modification of O-linked carbohydrate moieties on C1 inhibitor is not enabled for any method for changing the circulatory half-life of C1 inhibitor directly in vivo by a specific modification of its O-linked glycosylation, is not enabled a method of increasing or decreasing half-life of C1 inhibitor in vivo in any human subject or in any animal and/or a non-human transgenic animal as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reason of record as set forth in the previous office action mailed on 04/19/2006.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. In *re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of ordinary skill in the art has to go through "undue experimentation" in order to practice the invention.

Breadth of the claims, Guidance and the Existence of Working Examples and Predictability of the Art: The scope of the invention as claimed encompasses C1 inhibitor in or derived from any and all sources (plants, animals, mammals) that is modified under any conditions on its O-linked carbohydrate moieties (in vivo, ex vivo or in vitro) by any process (that occurs by naturally or induced gene mutations or

epigenetic processes) that changes its plasma circulatory half life of said inhibitor in any fashion (up or down). The scope of the claims further encompass a method of extending the blood circulatory half-life life of any and/or all glycoproteins and glycoprotein comprising compounds by removing one or more non sialylated O-linked carbohydrates from said glycoprotein in vitro or in vivo in any subject cell or in a non-human transgenic animal. As instantly claimed the in vivo modifications of glycoproteins encompasses gene therapy of humans in addition to enzyme therapy, drug therapy and etc.

The specification only provides guidance and/or evidences regarding a modification of recombinant human C1 inhibitor (rhC1INH) isolated from milk of a transgenic rabbit wherein the inhibitor protein was scialylated in vitro using scialylating enzymes ST3GalII alone (Example 1) or using both ST3GalII and ST3Gal I (Example 2) and their pharmacokinetic analysis by intravenous injection into rats (Example 3) wherein the injected modified protein exhibited increased half life. Further an in vitro modification of rhC1INH, by removal of non-sialylated O-glycans using a recombinant endo- α -N-Acetylgalactosaminidase enzyme (example 4) has also been described. Thus the Instant specification only provides guidance and/or evidences regarding modulation of plasma circulatory half-life of an in vitro modified C1 inhibitor (rhC1INH) with respect to its carbohydrate moieties. The specification further describes a method of modifying a C1 inhibitor (rhC1INH) on its O-linked carbohydrate moieties in vitro followed by an intravenous delivery into a rat to provide C1 inhibitor with an increased half-life in blood circulation

Besides in vitro modification of rhC1INH protein and its intravenous injection to measure the increased pharmacokinetics in a rat, the specification fails to disclose any changing of plasma half-life of C1 inhibitor by a direct and specific modulation of its O-linked glycosylations in vivo. Further it does not describe any specific examples of the broadly claimed method wherein a C1 inhibitor half-life is extended by modulating O-linked carbohydrate in vivo by expressing one or more glycosylation enzymes in any human or a non-human animal as claimed.

The applicant does not enable even a single of example of an enzyme or a gene or a drug therapy etc in any non-human animal for modulating directly in vivo the plasma circulatory half-life of C1 inhibitor in vivo and further does enable even a single method of increasing blood circulation half-life of any glycoprotein or glycoprotein comprising compound by removing any non-sialylated O-linked carbohydrate in vivo by expressing any enzyme in any animal. In the absence of enabled examples and/or representative number of enabled examples in the specification regarding in vivo modulation of O-linked glycosylation of specifically of C1 inhibitor commensurate with the breadth of the claims one of ordinary skill in the art would conclude that the invention is unpredictable and would require undue experimentation to practice the invention in its full scope.

At about the effective filing date of the present application art is unpredictable with regard to methods of increasing half-life of circulatory half-life of a specific glycoprotein or C1 protein in vivo by expressing an enzyme or by providing an exogenous gene coding for such enzymes. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of many therapeutic genes and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions etc in vivo.

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully carry out claimed specific glycosylation or deglycosylation of a targeted glycoprotein directly in vivo and increase or decrease its plasma or circulatory half-life. Difficulty is increased by the fact that the considered enzymes (e.g., ST3 gal I and ST3 Gal III, or endo-alpha-N acetyl-galactosaminidases etc) have broad specificity in terms of substrate proteins and hence one of ordinary skill in the art would not be able to specifically modulate glycosylation of a target protein molecules in vivo (for e.g. C1-inhibitor) and thus not be able to specifically modulate the half-life of said target protein only (which is an important criteria while treating a disease associated with any specific protein). Accordingly, in view of lack of teachings in the art or guidance

Art Unit: 1633

provided in the specification with regard to an enabled use of a method for specifically modulating circulatory half-life of C1 inhibitor or other target glycoproteins in vivo by directly expressing an enzyme/s wherein the enzyme specifically modifies O-linked glycosylation on said specific target glycoprotein, and in sufficient number of examples of glycoproteins as broadly claimed as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the best the specification as filed is found only enabled for a method of modulating plasma or circulatory half-life of C1 inhibitor by intravenous administration of a C1 inhibitor (e.g., rhC1INH) that is modified with respect to its O-linked carbohydrate moieties in vitro.

In Response to Arguments of 08/17/2006:

Applicant amends method claims. Applicant argues therefore concerns over the scope of the claim encompassing gene therapy for in vivo modulation of O-linked glycosylation is overcome because the amended claims restrict the scope of in vivo modulation to non-human transgenic animals only.

Applicants' arguments are however, found not persuasive because firstly the primary Claim 16 as amended still encompasses in vivo by co-expression of one or more enzymes (= exogenous genes for said enzymes) in a cell (=any cell, including human) and thus the scope of claims still is broad and encompasses gene therapy in humans in addition transgenic non-human animals. Secondly the applicants' product claims still encompass in its breadth in vivo modulation of glycosylation in all animals and further applicant has not described sufficient number of examples how this specific modulation of O-linked glycosylation in vivo in any animal is carried out. In the absence of enabled description of the broad claims with sufficient number of examples, one of skill in the art would find that it would require undue experimentation to practice the invention in its full scope. Hence the enablement rejection is maintained as above.

Claim Rejections - 35 USC § 103

Claims 1-13 and 16-22 stand rejected under 35 USC 103 (a) as being unpatentable over Paulson et al (1998, WO 98/31826), Shoenberger et al (1992, FEBS 314: 430-434), Wolf et al., (2001, protein expression and purification 22:414-421) and in view of Glaser et al (WO 92/03149) for the reason of record as set forth in the previous office action mailed on 04/19/2006.

In Response to Arguments of 08/17/2006:

Applicant argues that Paulson's reference is not relevant because he does not mention C1 inhibitors. Applicant further argues that 103 references provided (Shoenberger, Wolf and Glaser) do not expressly teach the importance of O-linked glycosylations in changing circulatory half-life of the C1 inhibitor.

However, Applicant's arguments are not found persuasive because firstly the Applicant's instant method claims 16-21 are broad and encompass all glycoproteins and all glycoprotein-comprising compounds and hence the applied art is still relevant. Secondly for the purpose of C1 inhibitor O-glycosylation modifications the Applicant uses the same generic methods described in Paulson for glycoproteins in general thus making it relevant with regard to claimed modulation of O-glycosylation of C1 inhibitor in particular. Fourthly Paulson by describing a generic method regarding protein glycosylations and their role in circulatory half-life of glycoproteins anticipates all glycoproteins (including C1 inhibitor O-linked modulation). Further Shoenberger, Wolf references clearly teach the C1 inhibitor activity modulation in the context of both N and O-glycosylations and the role of modulation O-glycosylations in hereditary diseases clearly indicates the importance of O-linked glycosidic moiety in the biological role of C1 inhibitor (which inherently encompasses circulatory half-life of C1 inhibitor). Thus the instant invention as claimed is obvious over the combination of cited references. Hence the rejection is maintained.

Conclusion:

No claim allowed.


Art Unit: 1633

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hirianna* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is **571 272-0548**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach*, may be reached at **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

Kelaginamane T. Hirianna

Patent Examiner

Art Unit 1633


SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER